CLINICAL

Resurrection of Preterm Labor Drug Evokes Questions of Fairness

Big prices for small-market biopharmaceuticals is nothing new. But when the market is centered around a public health concern, pricing can trigger contentious issues.

BY TOM MORROW, MD

Few public health priorities have received as much attention as maternal-fetal health. Preterm labor, in particular, is a concern that can result in any number of personal and societal burdens, and its prevention has been a staple of healthcare policy for more than half a century. When manufacture of an inexpensive drug that may prevent preterm labor is discontinued because of economies of scale and then reintroduced at a significant price increase, it raises questions not only of public health, but also of good corporate citizenship, regulatory authority, and the ability of society to reach national healthcare goals.

That scenario is now playing out, pitting a pharmaceutical company against physicians, patients, and payers. In a healthcare economy that is struggling to find a sustainable level of growth, how the market and regulators ultimately respond bears watching.

They're onto something

Preterm delivery is a serious public health problem. Preterm birth accounts for 85 percent of all perinatal morbidity and mortality at an estimated societal cost of $26 billion (Behrman 2007). Nationally, preterm birth affects about 12 percent of all newborns, or nearly 500,000 births.

The role of progesterone in preventing preterm birth has been the source of hypothesis and research for more than three quarters of a century. In 1934, investigators isolated progesterone from the corpus luteum, leading physicians to speculate that it was involved in the maintenance of pregnancy. Progesterone is a cholesterol-based sex steroid, and in normal pregnancy is believed to suppress immunity, prevent rejection of fetal cells, induce myometrial quiescence by suppressing contractile genes, promote relaxation of the uterus, suppress cytokines and prostaglandins, and reduce uterine response to oxytocin.

"What does FDA approval of a drug mean to the market? And will MCOs demand the use of a non-FDA approved drug?" asks Tom Morrow, MD.

In 1956, the U.S. Food and Drug Administration approved the first commercially available progestin, 17α-hydroxyprogesterone (17P). Marketed by Squibb Pharmaceuticals under the brand name Delalutin, the drug's initial FDA indication did not include pregnancy; it was approved for use in nonpregnant women for the treatment of uterine cancer, to manage amenorrhea and abnormal uterine bleeding, and as a test for estrogen production.

Several years later, a Canadian case study described the use of 17P as a progesterone replacement in several pregnant women whose tumorous ovaries were surgically removed (MacIntyre 1961). Other case studies followed, and Delalutin was soon used off-label for maintenance of pregnancy. But most of this use was based on small studies that, at times, yielded conflicting evidence.

In 1990, a meta-analysis of seven placebo-controlled trials of prophylactic use concluded that 17P was associated with a reduction in the occurrence of preterm birth (Keirse 1990). This finding stimulated the use of 17P, but questions remained as to who would actually benefit.

Delalutin remained on the market until 1999, when production was ended. Then, in 2010, CUSTO*pharm,* a product development company, filed a citizen's request asking the FDA to issue a statement as to whether Delalutin, was removed from the market because of efficacy

or safety concerns. The FDA concluded that neither was the case (Federal Register 2010), thus opening the door for drug makers to file an abbreviated new drug application (ANDA) to obtain marketing approval for Delalutin.

Seminal study

In a landmark study published in the *New England Journal of Medicine,* an injectable form of 17P in castor oil was compared with a castor oil placebo (Meis 2003). The goal was to determine whether 17P reduced the risk of preterm labor in women who had prior preterm delivery.

The double-blind, placebo-controlled, randomized trial, sponsored by the The National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, was performed at 19 academic and clinical centers in the United States. It enrolled women at 16–20 weeks of gestation. Weekly injections continued until delivery or the completion of 36 weeks of pregnancy, whichever came first. The primary endpoint was delivery prior to 37 weeks of gestation.

Started in April 1998, the trial was stopped abruptly 10 months later because the FDA ordered the drug supplier to shut down, prompting a product recall. The study was started afresh after investigators named another source for the study drug. Ultimately, 463 women were randomized. Results demonstrated a 36 percent rate of preterm delivery at less than 37 weeks in the 17P group compared with a 55 percent rate in the placebo group (P=.003). Subjects who received 17P also experienced decreased morbidity, along with significant reductions in rates of necrotizing enterocolitis, intraventricular hemorrhage, and the need for supplemental oxygen. The results led the American College of Obstetricians and Gynecologists (ACOG) to develop a guideline (ACOG 2009), widely followed since, that suggests if all eligible women received progesterone, 10,000 preterm births could be prevented annually.

Thus, despite a literature base that reaches back 50 years supporting the use of 17P for the prevention of preterm birth, an FDA-approved product has not been commercially available for more than a decade. To obtain 17P, physicians must order it from compounding pharmacies, which is how thousands of women each year receive this product.

David vs. Goliath

The economics of pharmaceutical manufacturing often results in the discontinuation of products such as 17P, and the only source for many of them is the compounding pharmacies. In the United States, there are at least 2,000 licensed and state-regulated compounding pharmacies represented by the International Academy of Compounding Pharmacists (IACP). The FDA's role is limited to regulating the manufacture of the base ingredients — in this case, the chemical 17P. The compounding pharmacy simply mixes the active drug into the inert oil for injection.

The retail price of branded 17P was set at $1,500 per dose, later reduced to $690 — for a drug available from compounders for $10 to $15.

Shortly after the Meis study was published, Adeza Biomedical Corp. met with the FDA to discuss submitting an ANDA for 17P for the prevention of preterm birth using the Meis data. The FDA, however, called the lack of follow-up data on the health of babies born to mothers who received 17OHP-C, the study drug, "a major concern." The FDA also wanted "complete chemistry, manufacturing, and control information" about the drug product, including its purity and potency. Adeza proceeded with the ANDA, seeking an indication for prevention of recurrent preterm delivery on the basis of the Meis study, and included analyses of the initial aborted study and the health of children born during the Meis trial.

Fast forward several years: Adeza was sold, and the rights to 17P eventually landed in the lap of KV Pharmaceuticals and its partner Ther-Rx. KV Pharmaceuticals pursued FDA approval of 17P under the brand name Makena. Last February, Makena received approval under the FDA's fast-track process. Drugs approved under this process must conduct postmarketing studies, so KV Pharmaceuticals is now enrolling patients for a study that will continue through 2016. It estimates the market for Makena at 140,000 women each year.

KV Pharmaceuticals then stunned the market when it announced a price of $7,500 per five-dose vial of 17P, or $1,500 per dose. The compounded version of the drug sells for roughly $10 to $15 per dose. KV Pharmaceuticals cited morbidity-cost comparisons, saying that "a preterm birth, including both inpatient and outpatient care, is more than $51,000."

KV Pharmaceuticals also sent letters to compounding pharmacies saying that it would ask the FDA to order them to stop making the compounded form of 17P. The IACP dismissed the letter as a "scare tactic."

Outcry over pricing

The pricing issue created a stir among physicians and health plans and in Congress. ACOG President Richard Waldman, MD, American

Academy of Pediatrics President Marion Burton, MD, and Society for Maternal-Fetal Medicine President George Saade, MD, complained that the "approximately $30,000-per-pregnancy" cost of Makena amounts to a $4.2 billion burden on the healthcare system — one that would fall primarily on the backs of cash-strapped Medicaid programs. They further stated that manufacturer-offered financial assistance was insufficient and did not extend to certain groups of women.

Karen Ignagni, president of America's Health Insurance Plans, has asked the FDA to provide clear guidance to patients and physicians on its stance with respect to compounding pharmacies. And on Capitol Hill, Ohio Sen. Sherrod Brown called for a federal investigation into the potential effect of these costs on taxpayers and the Medicaid program. He also asked that the Federal Trade Commission initiate an investigation into any potential anticompetitive conduct arising out of KV Pharmaceuticals' actions.

In late March, the FDA said it would not take enforcement action against pharmacies that compound hydroxyprogesterone caproate "unless the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards for compounding sterile products." Two days later, KV Pharmaceuticals/TherRx said it would reduce the price to $690 per shot. Some critics called the reduction a step in the right direction, but it did not satisfy everyone — including the March of Dimes, which terminated a fundraising partnership with KV Pharmaceuticals.

Relevant issues

17P has become an inexpensive standard of care for the maintenance of pregnancy in women with a history of preterm labor. It has been studied for decades and, until recently, was affordable to people even in the lowest socioeconomic levels. Now, a company using data derived from a taxpayer-funded study has obtained FDA approval for a drug that is available through compounding pharmacies. The company also attempted to use the FDA's legal authority to insist that less-expensive alternative sites be ordered to cease production of this product.

Numerous specialty societies have asked for a reconsideration of pricing, and even Congress threatens to become involved. Managed care organizations have, for the most part, remained publicly silent, but are certain to take note, at least financially.

The fact that the FDA has jurisdiction over state-regulated compounding pharmacies but has publicly chosen not to exercise its authority seems to have created an uneasy ceasefire. Obviously, without the government enforcing its authority, the manufacturer faces a huge pricing issue that the market is certain to notice.

Questions remain: What does FDA approval of a drug mean to the market when a less-expensive, nonFDA-approved alternative exists? Will MCOs demand the use of a nonFDA-approved drug? Will KV Pharmaceuticals ask the courts to get involved? Will the FDA change its stance? Will patients be kept in the middle?

Any or all of these scenarios are possible, but one compounding pharmacy has offered a potential long-term solution: Offer a product with a similar, but different, composition.

The approved drug is 250 mg of 17OHP-C in 1 mL castor oil with 46 benzyl benzoate and 2 percent benzyl alcohol. Pharmaceutical-grade sesame oil has long been an alternative for compounding 17P for physicians who choose not to use castor oil, the safety of which has not been studied for the prevention of preterm labor and which anecdotal reports suggest can actually induce labor. Sesame oil offers the same slow absorption properties as castor oil and is widely used.

If 17P were compounded using sesame oil, it would not be identical to an FDA approved drug — potentially muting a battle that certainly will raise its head again.

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Disclosure

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